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ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com
andrea.ryan@sanofi-aventis.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/574,416 | GRUENEBERG ET AL. | |
| | Examiner | Art Unit | |
| | Kimberly Chong | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8 and 16-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-15* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Group IV claims 1-7 and 9-15 and SEQ ID Nos. 4, 7 and 8 in the reply filed on 11/29/2007 is acknowledged. The traversal is on the ground(s) that there is not a serious search burden because the inventions, while acknowledging they are patentably distinct, have acquired a similar status in the art in view of their identical classification. This is not found persuasive because the inventions would require employing different search queries. For example, a search of a retroviral vector comprising a U6 promoter having SEQ ID No. 7 would not necessarily reveal art for a H1 promoter having SEQ ID No. 14. Likewise, a search for a retroviral vector comprising a polylinker having SEQ ID No. 4 would not necessarily reveal art for a polylinker having any of SEQ ID Nos. 1-3 or 5-6. Moreover, a search for the different sequences all having different SEQ ID Nos. would require different search queries and therefore would be considered a serious search burden.

The requirement is still deemed proper and is therefore made FINAL.

### *Status of the Application*

Claims 1-22 are pending. Claims 1-7 and 9–15 are currently under examination. Claims 8, 16-22 and non-elected material are withdrawn as being drawn to a non-elected invention. SEQ ID Nos. 4 and 8 are free of the prior art searched and made of record.

### *Information Disclosure Statement*

The submission of the Information Disclosure Statement on 08/27/2007 is in compliance with 37 CFR 19.7. The information disclosure statements have been considered by the examiner and signed copies have been placed in the file.

### *Sequence Compliance*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below: Pages 3, 5 and 15 of the specification recite sequences that do not have the required sequence identifier. A complete response to this office action must correct the defects cited above regarding compliance with the sequence rules and a response to the action on the merits which follows.

The aforementioned instance of failure to comply is not intended as an exhaustive list of all such potential failures to comply in the instant application. Applicants are encouraged to thoroughly review the application to ensure that the entire application is in full compliance with all sequence rules. This requirement will not be held in abeyance.

### *Claim Objections*

Claims 1 and 11 are objected to because of the following informalities: Claims 1 and 11 are grammatically incorrect because it appears to be missing the word "to"

between *complementary* and *a* in line 8 of the claim 1 and line 30 of claim 11.

Appropriate correction is required.

Claims 2, 3, 11, 12, 14 and15 are objected to as reciting non-elected subject matter. Claims 2, 3, 11, 12, 14 and15 should be rewritten deleting any non-elected subject matter.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 11 recite the dsRNA comprises a sense portion that is complementary [to] a portion of the antisense strand of the target gene". There is lack of antecedent basis for "the antisense strand of the target gene" because the target gene is not described as having a sense and an antisense strand. Further, it is not clear what is meant by the sense portion of the dsRNA being complementary to antisense strand of the target gene since target genes are not described as having a sense strand and an antisense strand.

Claims 1 and 11 are further indefinite because the claim recites "the double stranded RNA folds back upon itself." It is unclear what is meant by the dsRNA folding back upon itself. The molecule is already double stranded having a sense and

antisense strand that anneal and therefore it is unclear how the molecule can then also fold back upon itself. For purposes of prior art, claim 1 will be interpreted to comprise a target specific dsRNA having a sense and an antisense strand that are complementary to each other.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 15 recite the word Blasti and this word is not defined in the instant specification and as such the meets and bounds of the claims can not be determined without assumption. It would appear the word Blasti is an abbreviated form of a marker gene Blasticidin S deaminase but this cannot accurately be determined without assumption since Blasti does not appear to be a common abbreviation of a Blasticidin S deaminase gene.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Devroe et al. (BMC Biotechnology August 2002).

The claims are drawn to a retroviral vector comprising a promoter, a polylinker region, a target gene specific insert comprising a dsRNA having a sense and antisense strand, wherein the sense and antisense strand each comprise a length of 19-30, 19-25 or 19-23 nucleotides.

Devroe et al. teach a retroviral vector comprising a U6 promoter, a polylinker sequence and a target gene specific insert sequence wherein the sequence is capable of forming a hairpin dsRNA (see Figure 1). Devroe et al. teach the dsRNA is targeted to a NDR gene or a p75 gene wherein each strand is 20 nucleotides in length (see pages 4 and 5). The instant specification teach a polylinker sequence region is a sequence that comprises a plurality of restriction sites. The retroviral vector comprising a region

having restriction sites flanking the promoter and hairpin dsRNA would constitute a region having a plurality of restriction sites and therefore meets the limitations of the instant claims.

Thus, Devroe et al. anticipates claims 1 and 4-6 of the instant invention.

Claims 1, 4-6 and10 are rejected under 35 U.S.C. 102(a) as being anticipated by Barton et al. (PNAS November 2002).

The claims are drawn to a retroviral vector comprising a promoter, a polylinker region, a target gene specific insert comprising a dsRNA having a sense and antisense strand, wherein the sense and antisense strand each comprise a length of 19-30, 19-25 or 19-23 nucleotides and wherein said cell has said target gene in its genome.

Barton et al. teach a retroviral vector comprising a promoter, a polylinker sequence and a target gene specific insert sequence wherein the sequence is capable of forming a hairpin dsRNA (see Figure 1). Barton et al. teach the dsRNA is targeted to a p53 gene in human 293 cells (see page 14943), which is a gene found in mammalian cells, wherein each strand is 19-21 nucleotides in length (see page 14943 which references Brummelkamp et al. which teach the dsRNA construct, cited as reference 7). The instant specification teaches that a polylinker sequence region is a sequence that comprises a plurality of restriction sites. The retroviral vector comprising a region having restriction sites flanking the hairpin dsRNA taught by Barton et al. would constitute a region having a plurality of restriction sites and therefore meets the limitations of the instant claims.

Thus, Barton et al. anticipates claims 1, 4-6 and 10 of the instant invention.

Claims 1, 4-7 and 9-10 rejected under 35 U.S.C. 102(e) as being anticipated by Verma et al. (US 2004/0234504).

The instant claims are drawn to a retroviral vector comprising a promoter, a polylinker region, a target gene specific insert comprising a dsRNA having a sense and antisense strand, wherein the target gene is an oncogene, wherein the sense and antisense strand each comprise a length of 19-30, 19-25 or 19-23 nucleotides and wherein said cell has said target gene in its genome.

Verma et al. teach a lentiviral vector comprising a promoter and a siRNA sequence and further comprising nucleotides sequences comprising restrictions sites i.e. polylinker regions (see Figure 1 and claims 1, 2, 6, 10-15 and 18). Verma et al. teach the lentiviral vector can comprise pol III promoter such as a U6 promoter instead of a CMV promoter (see Figure 10 and paragraph 0058). Verma et al. teach the siRNA comprises strands of 19-22 nucleotides in length (see paragraph 0038). Verma et al. further teach the siRNA can target cancer genes and transcripts of malignant conditions (see paragraph 0017-0018).

Thus, Verma et al. anticipates claims 1, 4-7 and 10.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-7 and 9-11 rejected under 35 U.S.C. 103(a) as being unpatentable over Devroe et al. (BMC Biotechnology August 2002), Noonberg et al. (US Patent NO. 5,624,803) and Chang et al. (Current Gene Therapy, 2001, 1: 237-251).

The claims are drawn to a retroviral vector comprising a promoter, a polylinker region, a target gene specific insert comprising a dsRNA having a sense and antisense strand, wherein the promoter is a U6 promoter sequence of SEQ ID No. 7, wherein the polylinker region comprises a nucleotide sequence of SEQ ID NO. 4, wherein the sense and antisense strand each comprise a length of 19-30, 19-25 or 19-23 nucleotides, wherein the target gene is an oncogene, wherein the retroviral vector is a modified Lentivirus comprising a RRE, a U6 promoter of SEQ ID No. 7, wherein said cell has said target gene in its genome, wherein the Lentivirus further comprises a Blasti reporter gene.

Devroe et al. teach a retroviral vector comprising a U6 promoter, a polylinker sequence and a target gene specific insert sequence wherein the sequence is capable of forming a hairpin dsRNA (see Figure 1). Devroe et al. teach the dsRNA is targeted to a NDR gene or a p75 gene wherein each strand is 20 nucleotides in length (see pages 4 and 5). The instant specification teaches a polylinker sequence region is a sequence that comprises a plurality of restriction sites. The retroviral vector comprising a region having restriction sites flanking the promoter and hairpin dsRNA would constitute a region having a plurality of restriction sites and therefore meets the limitations of the instant claims. Devroe et al. do not specifically teach a U6 promoter sequence of SEQ

ID No. 7 and do not teach using lentiviral vectors wherein the CMV promoter is removed and a REV element is present.

Noonberg et al. teach a U6 promoter sequence and teach efficient expression of nucleic acids using this promoter. The promoter sequence taught by Noonberg has one nucleotide mismatch as compared to the instantly claimed sequence (see included sequence alignment) however this nucleotide mismatch in the instantly claimed sequence does not render the U6 sequence and its use in an expression vector patentably distinguishable over the sequence taught by Noonberg et al., absent evidence to the contrary.

Chang et al. teach the use of lentiviral vectors as an efficient gene delivery vehicle and teach lentiviral vectors are advantageous over similar vectors systems in that they can infect non-dividing cells (see page 237). Chang et al. teach all lentiviral vectors need the REV element that interacts with the REV-response element for efficiently cytoplasmic transport in cells (see page 240-241).

It would have been obvious to one of skill in the art to use a lentiviral vector to express the dsRNA taught by Devroe et al. It would have further been obvious to one of skill in the art to use U6 promoter instead of the CMV promoter in a lentiviral vector and to incorporate a REV element as taught by Chang et al.

One of skill in the art would have been motivated to use a lentiviral vector given Chang et al. teach the advantages of lentiviral vectors, such as being able to infect non-dividing cells. One would have wanted to use the most efficient viral vector system for delivery of the dsRNA taught by Devroe et al. for the purpose of silencing gene

expression. Further, one would have wanted to use the U6 promoter sequence taught by Noonberg et al. given Noonberg et al. teach use of said promoter efficiently drives expression of oligonucleotides in cells. Chang et al. teach that for efficient cytoplasmic transport of the lentiviral vector in cell, the REV element needs to be present in the vector to allow the REV/RRE interaction to occur, therefore one of skill in the art would have been motivated to incorporate a REV element into a lentiviral vector.

One would have expected to be able to use a lentiviral vector for delivery of a dsRNA given Chang et al. teach said vectors are well known to be efficient gene delivery vehicles and further one would have expected to be able to incorporate a REV element because Chang et al. teach the usefulness of said element in retroviral vectors.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 2, 4-7 and 9-11 rejected under 35 U.S.C. 103(a) as being unpatentable over Verma et al. (US 2004/0234504), Noonberg et al. (US Patent NO. 5,624,803) and Chang et al. (Current Gene Therapy, 2001, 1: 237-251).

The claims are drawn to a retroviral vector comprising a promoter, a polylinker region, a target gene specific insert comprising a dsRNA having a sense and antisense strand, wherein the promoter is a U6 promoter sequence of SEQ ID No. 7, wherein the polylinker region comprises a nucleotide sequence of SEQ ID NO. 4, wherein the sense and antisense strand each comprise a length of 19-30, 19-25 or 19-23 nucleotides,

wherein the target gene is an oncogene, wherein the retroviral vector is a modified Lentivirus comprising a RRE, a U6 promoter of SEQ ID No. 7, wherein said cell has said target gene in its genome, wherein the Lentivirus further comprises a Blasti reporter gene.

Verma et al. teach a lentiviral vector comprising a promoter and a siRNA sequence and further comprising nucleotide sequences comprising restrictions sites i.e. polylinker regions (see Figure 1 and claims 1, 2, 6, 10-15 and 18). Verma et al. teach the lentiviral vector can comprise a pol III promoter such as a U6 promoter instead of a CMV promoter (see Figure 10 and paragraph 0058). Verma et al. teach the siRNA comprises strands of 19-22 nucleotides in length (see paragraph 0038). Verma et al. further teach the siRNA can target cancer genes and transcripts of malignant conditions (see paragraph 0017-0018). Verma et al. do not specifically teach a U6 promoter sequence of SEQ ID No. 7 and do not teach a lentiviral vectors comprising a REV element.

Noonberg et al. teach a U6 promoter sequence and teach efficient expression of nucleic acids using this promoter. The promoter sequence taught by Noonberg has one nucleotide mismatch as compared to the instantly claimed sequence (see included sequence alignment) however this nucleotide mismatch in the instantly claimed sequence does not render the U6 sequence and its use in an expression vector patentably distinguishable over the sequence taught by Noonberg et al., absent evidence to the contrary.

Chang et al. teach the use of lentiviral vectors as an efficient gene delivery vehicle and teach lentiviral vectors are advantageous over similar vectors systems in that they can infect non-dividing cells (see page 237). Chang et al. teach all lentiviral vectors need the REV element that interacts with the REV-response element for efficiently cytoplasmic transport in cells (see page 240-241).

It would have been obvious to one of skill in the art to use the U6 promoter taught by Noonberg et al. and to incorporate a REV element as taught by Chang et al.

One of skill in the art would have wanted to use the U6 promoter sequence taught by Noonberg et al. given Noonberg et al. teach use of said promoter efficiently drives expression of oligonucleotides in cells. Chang et al. teach that for efficient cytoplasmic transport of the lentiviral vector in cell, the REV element needs to be present in the vector to allow the REV/RRE interaction to occur; therefore one of skill in the art would have been motivated to incorporate a REV element into a lentiviral vector.

One would have expected success at using the U6 promoter taught by Noonberg for expression of a siRNA given Noonberg et al. teach efficient expression of a oligonucleotide expressed from a vector comprising a U6 promoter. One would have expected to be able to use a lentiviral vector comprising a REV element for delivery of a dsRNA given Chang et al. teach said vectors are well known to be efficient gene delivery vehicles and the REV element is essential for cytoplasmic transport.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kimberly Chong/
Examiner
Art Unit 1635